REVIEW ARTICLE

The Role of Oxidative Stress and Inflammation in Prediabetes: A Review

Fatma S.A Saghir[1], Farrah Shafeera Ibrahim[1], Zulkhairi Amom[1], Lekhsan Othman[2]

[1] Department of Basic Sciences, Faculty of Health Sciences, Universiti Teknologi MARA, Puncak Alam Campus, 42300 Puncak Alam, Selangor, Malaysia
[2] Jeffrey Cheah School of Medicine, Monash University Malaysia, Jalan Lagoon Selatan, Bandar Sunway, 47500 Subang Jaya, Selangor

ABSTRACT

Prediabetes is a condition in which blood glucose level is above the normal but below the diagnostic value of diabetes mellitus. Hyperglycaemia can upregulate markers of chronic inflammation and contribute to the overproduction of reactive oxygen species (ROS), which ultimately causes increased oxidative stress. This leads to beta-cell dysfunction and insulin resistance, which are involved in the pathogenesis of prediabetes status. Proper treatment of hyperglycaemia, inhibition of ROS overproduction, and suppression of inflammation are crucial for delaying the onset of diabetes. Therefore, it is essential to determine and understand the mechanisms involved in prediabetes. This review discusses the relationship between oxidative stress and prediabetes, along with the inflammation's role in prediabetes. Additionally, the effects of some biomarkers of oxidative stress in prediabetes, inflammatory markers, and their influence on chronic inflammation are also briefly reviewed. Finally, the role of antioxidant and anti-inflammatory markers are discussed.
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Corresponding Author:
Farrah Shafeera Binti Ibrahim, PhD
Email: shafeera@uitm.edu.my
Tel: +603-32584362

INTRODUCTION

Prediabetes is a state whereby the glucose level in blood is more than the average value but still less than the diabetes mellitus level (1-4). According to the American Diabetic Association (ADA), prediabetes is diagnosed when impaired fasting glucose (IFG) level is between 100 to 125mg/dl, and impaired glucose tolerance (IGT) is between 140 to 199mg/dl (1-7).

Prediabetes will develop into type 2 diabetes mellitus (T2DM) over time (1,6-8). The glucose intolerance can start 10 – 12 years in prediabetes individuals before the development of diabetes. Therefore, early diagnosis and treatment for prediabetes are important to delay or prevent the onset of diabetes, as prediabetes is a transitional and reversible state (6,9-11). Prediabetes cases are estimated to be up to 472 million by the year 2030, and about 70% of prediabetes cases will be developed into diabetes. Around 578 million people worldwide will be diagnosed with diabetes by 2030 and are expected to reach about 700 million by 2045 (12). Prediabetes patients are expected to suffer from many complications, for instance, peripheral vascular diseases, coronary artery diseases, and cerebrovascular incidents (4-6,13-15). In other words, undiagnosed prediabetic people are at risk for developing full blown diabetes, heart attack and stroke (2,7,11,14,16-19).

Many risk factors influence prediabetes, including hyperlipidaemia, abdominal obesity, smoking, alcohol consumption, hypertension, genetic disorders, and high caloric diets (2,20-22). Dietary control and exercise are the recommended interventions for prediabetes patients to prevent progress to T2DM; however, to bring blood glucose back to normal level would take a long time (17,19,22-24).

Inflammation and oxidative stress are known to be present in prediabetes patients and predispose them to dyslipidaemia and cardiovascular diseases (4,5,25). Oxidative stress and inflammatory components are also considered risk factors for peripheral vascular diseases (26).

The pathogenesis of prediabetes is associated with oxidative stress and inflammation due to high levels of free radicals and low levels of antioxidants, which can lead to insulin resistance (1,8,13,25). The flow chart in

Fig. 1 shows the role of oxidative stress and inflammation in prediabetes.

Prediabetes is considered as an asymptomatic period preceding the full-blown diabetes mellitus (3,17,24). This stage could be the time where some therapeutic interventions, with perhaps early investigations, would successfully prevent the progress of prediabetes into T2DM. Also, the interventions would prevent those complications like cardiovascular diseases, one of the major causes of death worldwide (5,9,17,18,24,25,27).

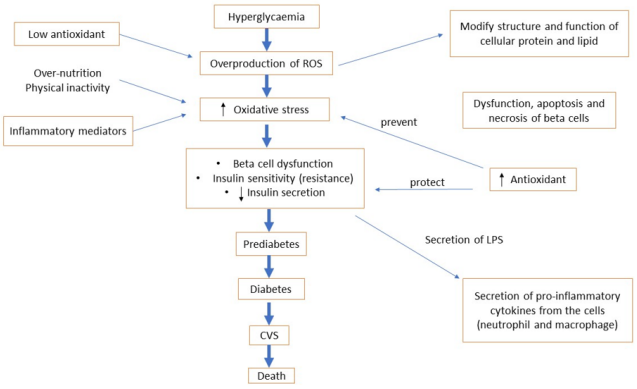

Figure 1: Pathogenesis of prediabetes

Currently, pharmacological agents are used for prediabetic patients such as metformin. Their mechanism of action is to inhibit the inflammation by inhibiting the oxidative stress. However, a healthy life is still recommended for successful management (17,21,28,29). Recently, many scientists have been focusing on investigating natural products in terms of their antidiabetic, antioxidants, and anti-inflammatory activities in correlation to prediabetes status (2,6,21,23,30,31).

Although studies regarding the role of oxidative stress and inflammation in correlation with the pathogenesis of prediabetes are very limited, this review will focus on these mechanisms.

OXIDATIVE STRESS IN PREDIABETES

The Relation Between Oxidative Stress and Prediabetes

Free radicals or oxidants such as hydroxyl radical (OH) are the natural product of body metabolism and play an essential role in cellular homeostasis. Typically, these oxidants can be triggered by many factors, such as high blood glucose level, smoking, alcohol consumption, and ultraviolet ray (32). A sufficient amount of antioxidants is required to regulate and overcome the upregulation of these oxidants (32). Oxidants are related to many pathological disorders because of a phenomenon called 'oxidative stress' which means an increased amount of reactive oxygen species (ROS) in the human body (32).

Hyperglycaemia leads to the generation of excess free radicals, thus increasing oxidative stress. Subsequently, high levels of ROS alter the structure and function of cellular proteins, carbohydrates, lipids, and DNA (8,13,33). As a result, there will be dysfunction, apoptosis, and necrosis of pancreatic beta-cells and inhibition of sensitivity in the liver, skeletal muscles, and adipose tissues (8,13). Therefore, suppression in insulin secretion (beta-cell dysfunction) and sensitivity is a statute of prediabetes that might develop into diabetes or/ and cardiovascular complications; death most probably is the end of this scenario (8,18). Malondialdehyde (MDA) is a biomarker of lipid peroxidation, which correlates to monitoring ROS production. MDA has been demonstrated as a marker of oxidative stress (13,34).

The oxidative stress depends on the deficiency of antioxidant defence mechanism (1,8). Examples of antioxidants are polyphenolics, polysaccharides, and vitamin C. An antioxidant can neutralise a rampaging free radical via donating an electron; therefore, the free radical becomes less or not harmful. The antioxidant level can be used to reflect the level of oxidative stress (13). Excessive accumulation of free radicals and low antioxidant levels are observed in the pathogenesis of prediabetes (1,8).

A study in Saudi Arabia has observed low antioxidant level in prediabetes people which is considered as a marker of oxidative stress, along with dyslipidaemia, obesity, and physical inactivity. In that study, there was a significant decrease in serum total antioxidant status (TAS) level in prediabetes compared to normal people (16).

The effect of controlling blood glucose through diet and its impact on oxidative stress in prediabetes has been tested (1). Oxidative stress was improved in prediabetes men who underwent five weeks of early time-restricted feeding. The study also reported that insulin level, insulin sensitivity, beta-cell responsiveness, and blood pressure were enhanced along with oxidative stress (1).

In yet another study, the oxidative stress markers were measured in prediabetes and newly diagnosed cases of diabetes in comparison to normal subjects. The results revealed that cellular damage starts prior to the onset of diabetes (33).

Biomarkers of Oxidative Stress in Prediabetes

Oxidative stress is a condition where there is an imbalance between oxidants and antioxidants, which cause oxidative damage to cellular structure and function. Biomarkers are the products of oxidative damage in the body. Identifying and investigating these biomarkers might be useful in the process of avoiding prediabetes situations (26,35). The following are some of the oxidative stress biomarkers related to prediabetes: 8-hydroxy-2'-deoxyguanosine (8-OHdG), malondialdehyde (MDA), and glutathione (GSH).

8-hydroxy-2′-deoxyguanosine (8-OHdG)
8-OHdG is a biomarker of oxidative stress in prediabetes and diabetes mellitus, which results mainly from cellular DNA damage; it is the most frequently detected in prediabetes and diabetes mellitus (9,13,26,33). A recent study showed a significant increase of this marker in blood samples of 200 prediabetes compared to 200 control subjects (13). Another previous study had similar findings, in which urine samples showed a significantly increase in the level of 8-OHdG in prediabetic subjects compared to control cases (9,33).

Furthermore, there was significantly increase in the level of 8-OHdG in prediabetes people with glucose intolerance. This would happen due to excessive production of ROS, which means an increase in the oxidative stress in response to high blood glucose level. Increased ROS will be affecting cellular structure and functions, particularly damaging the DNA. Thus, increased levels of 8-OHdG reflect an increase in the degree of oxidative stress and progressing of prediabetes condition toward diabetes (13,33). Therefore, early detection of oxidative stress biomarkers related to prediabetes such as 8-OHdG might be the key to treating prediabetes people and stopping the mechanism of converting to T2DM and its complications (9,26).

Malondialdehyde (MDA)
Malondialdehyde (MDA) is also a biomarker in prediabetes, related to the increase in oxidative stress. MDA is produced due to lipid peroxidation, which results from oxidative stress (35). In fact, the MDA level is significantly raised in prediabetes subjects with glucose intolerance. This could happen due to hyperglycaemia, where oxidation of glucose leads to generation of free radicals, then lipid's destruction (13). Consequently, lipid peroxidation supresses the cell membrane's physiological role, affecting its permeability and progress to cardiovascular problems (13,35). Evidence showed a significant increase in serum level of MDA in prediabetic patients compared to control individuals (13,34).

Glutathione (GSH)
Reduced GSH is the most important endogenous antioxidant and plays a vital role in detoxifying ROS and preventing ROS-induced cellular damage, thus providing protection against oxidative stress. In other words, any condition associated with excessive ROS will decrease GSH levels. Moreover, GSH acts as a substrate to glutathione peroxidase-1 (Gpx-1), which deficiency has been shown to be associated with increased risk for the development of coronary artery diseases and cardiovascular events (13).

Antioxidants (AOXs) in Prediabetes
Pathogenesis of prediabetes involves increased levels of free radicals but decreased antioxidant (AOXs) levels in the blood. Normally a free radical is neutralised when an AOXs donates an electron to it, minimising the damage that would result (1). AOXs can counterbalance an excess of ROS, halting the increase in oxidative stress. Thus, the importance of AOXs is to delay or prevent the damage that would happen due to the oxidative stress (35).

AOXs such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX) are produced naturally in the human body. AOXs can also be obtained from exogenous sources; a study suggests that prediabetes would be improved in response to consumption of food rich in AOXs because of its protective effect on beta-cells of the pancreas (1). Moreover, serum total antioxidant status (TAS) level in prediabetes is considered an appropriate marker of oxidative stress. There was a significant reduction in TAS in prediabetes compared to those with normal blood glucose levels (16).

INFLAMMATION IN PREDIABETES

The Relation Between Inflammation and Prediabetes
Insulin resistance due to oxidative stress leads to the escape of lipopolysaccharides (LPS) from the intestine into the blood. Then, LPS activates neutrophils and macrophages by binding with receptors on their surfaces, called pattern recognition receptors (PRR), such as toll-like receptor 4 (TLR4). This results in the secretion of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumour necrosis factor-alpha (TNFα) from those cells. Besides, low-density lipoprotein (LDL) binds to the PRRs on the macrophages, which leads to the release of more pro-inflammatory cytokines. Meanwhile, LDL bind to cluster differentiation 36 (CD36) on the platelet membrane and activate the platelet. After that, it releases one more inflammatory mediator known as cluster differentiation 40 ligand (CD40-L) (21).

Insulin resistance is commonly developed in some cases where the normal function of adipose tissue is disturbed, such as in obesity. This is due to increased secretion of both pro-inflammatory mediators and free fatty acids (21,3).

Increased plasma levels of biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), and fibrinogen indicate the subclinical degree of inflammation in prediabetes; they have already increased before T2DM onset. Alteration of the inflammatory response was observed according to the glucose status, whereby IL-1RA and CRP were highly increased in prediabetes compared to normoglycemic subjects (36).

Inflammatory Markers
Inflammation is part of the immune system to defeat against foreign materials and microorganisms. Inflammation is involved in the pathophysiology of many diseases and conditions such as prediabetes and diabetes mellitus; the cytokines might help identify prediabetes cases at

risk of developing T2DM and complications (3,26,37). The following are some inflammatory markers related to prediabetes: interleukin-6 (IL-6), C-reactive protein (CRP), and fibrinogen (38,39).

Interleukin-6 (IL-6)

IL-6 (major pro-inflammatory cytokine) production is induced by high blood glucose levels in the prediabetes group (3,5). Glycation end-products due to hyperglycaemia lead to progression of chronic inflammation. Additionally, IL-6 inhibits tyrosine phosphorylation and stimulates serine phosphorylation, resulting in impaired insulin sensitivity and resistance. This is related to increased lipolysis and decreased glucose uptake in the adipose tissue. Prediabetes serum samples have showed increase in IL-6 compared to control subjects (5). An increase of pro-inflammatory cytokines is related to insulin resistance, and the cytokines elevate in prediabetic individuals before the onset of T2DM (3,21).

C-reactive protein (CRP)

High sensitivity C reactive protein (hs-CRP) is a potential biomarker of subclinical inflammation, although it has a short life span of about 18 hours. CRP is known to be increased in case of hyperglycaemia. Besides, CRP is a well-known cardiac marker of pathological conditions in the cardiovascular system (3,13,26,34). It has been reported that prediabetic subjects demonstrated high level of hs-CRP compared to controls (13).

Fibrinogen

Fibrinogen is a plasma protein that contributes to the haemostasis mechanism and increases in the systemic response to chronic inflammation. Fibrinogen is activated by interleukin-6 (IL-6) (40). There was a significant increase in fibrinogen when comparing prediabetic and normoglycemic patients. Besides, it could be involved in the pathogenesis of prediabetes and diabetes.

CONCLUSION

In prediabetes, ROS increases with low levels of antioxidants. This results in impaired cellular structure and function, due to damage in carbohydrates, proteins, lipids, and DNA in the human body. Measuring the quantity of ROS is done through evaluation of oxidative stress biomarkers. Those biomarkers such as increased 8-OHdG, increased MDA and decreased GSH play an important role in development of prediabetes condition. Meanwhile, inflammation has important impact on the pathogenesis of prediabetes, through some inflammatory markers such as IL-6, C-reactive protein, and fibrinogen.

Deep understanding of oxidative stress and inflammation as the underlying causes of prediabetes might open the doors to early diagnosis and treatment of prediabetes, preventing the progress of this condition into type 2 diabetes mellitus. From this review, the impact of oxidative stress and inflammation may gain more popularity in the future.

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